Cariology Clinical Trials

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Cariology Clinical Trials; What are, and should we, be looking at?

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Abstract

Randomised control trial (RCT) methodology has compared interventions for prevention and management of dental caries since the late 1960s. Despite almost 50 years and evidence of significant wastage within the wider biomedical research field, there has been little investigation into what works well and where weaknesses lie. This paper summarises systematic review findings of cariology clinical trials, focussing on interventions and outcomes as two important areas within trial design and analyses. Examples illustrate some challenges with intervention delivery fidelity, outcome analyses and intervention co-production.

Trial design stage choices are critical in ensuring optimum information is obtained when testing interventions. Intervention choice, outcome choice and analyses are particularly important and cariology trials have specific issues associated with them. A systematic search and review of cariology RCTs, found 650 RCT reports. Social Network Analysis of interventions revealed: a high degree of separation between prevention and management trials; gaps in clinically important comparisons; a tendency to compare within groups e.g. comparison of interventions within the same, rather than different, levels of invasiveness. Outcomes measured for the same trial reports show: a focus on restoration performance and individual/population caries burden; growing use of carious lesion activity and economic related outcomes; and sparse, although growing use of, patient-reported/ patient-centred outcomes.

Fidelity of adherence to complex interventions can be challenging to measure but is important in interpreting trial findings. Involving target populations in intervention design, delivery and relating it to the planned rollout, are opportunities to ensure intervention relevance and improve uptake. Outcomes' analyses should consider minimum clinical important difference and outcome relevance for the target population.

Factors underlying trialists' comparator and outcome choice need to be identified, and there is a need to ensure that there is a minimum dataset of outcomes to allow combination and comparisons of trial data for systematic review.

Keywords: dental caries, clinical studies/ trials, restorative dentistry, preventive dentistry

Introduction

The first controlled clinical trial, carried out by James Lind in 1747, investigated whether citrus fruit could treat the symptoms of scurvy (Trohler 2005). It took a further 200 years, until 1948, before the first modern medical randomised controlled trial (RCT) was conducted (Crofton 2004) looking at Streptomycin for pulmonary tuberculosis (Yoshioka 1998). The RCT is considered the best way to test treatments. However, they are complex, expensive, time-consuming and difficult to carry out to a high standard. The challenges in producing high quality, relevant and useful research are manifold (Heneghan et al. 2017). The RCT is often talked about as a single entity, however, it comprises various parts, each of which, at the design,

execution, evaluation and write up stage is subject to choices which can affect result of the trial or its interpretation. Discussion and recommendations about methods to ensure a trial is successfully conducted have been more limited; for example, which methods within the RCT design are best in which situation (Ioannidis et al. 2014). It is ironic that there has been so little investigation into how to make trials as efficient and high quality as possible, leaving trial design and process lacking in a credible evidence-base. Two key points where decision making is critical are the areas of intervention choice and outcomes/ outcome measures' selection and analyses (Heneghan et al. 2017).

Clinical trials in cariology often do not have well-defined interventions and definite endpoints (Lamont et al. 2015). This paper will present some evidence on caries trials' methodologies related to interventions and outcomes over the last 50 years, raise awareness of complexities of both intervention design/ implementation (Stamm 2004) and outcome choice, though the example of two large-scale UK NIHR funded clinical RCTs (FiCTION and BRIGHT) looking at the prevention and management of dental caries and carious lesions.

Why does this matter?

Ideally, evidence flows seamlessly from novel discovery to evaluation in several primary clinical trials (Innes et al. 2016), the results of which are synthesised into systematic reviews which then inform practice guidelines that are then translated, through practitioners' daily care, into improved patient outcomes. However, the flow isn't always smooth with significant inefficiencies and wastage in the business of evidence production (Macleod et al. 2014). Back in 1747, it took 42 years for James Lind's work to translate into the Naval "Sick and Hurt Board" introducing citrus fruits to ships (Trohler 2005). Global life sciences research cost around US$240 billion in 2010. Furthermore, less than half of the biomedical literature that reaches the stage of publication is estimated to be of sufficient quality (in conduct and reporting) to be fit for purpose. Overall wastage within the research system is around US$200 billion; around 85% of the initial investment (Chalmers and Glasziou 2009). The figure remains unquantified as a whole for oral and dental research but the same problem of poor quality trials and their reporting is well known (Fleming et al. 2014; Lucena et al. 2017; Pandis et al. 2014; Rajasekharan et al. 2015; Sandhu et al. 2015). There is no reason to believe that the relative magnitude of the problem of waste is likely to be different from the rest of the biomedical field.

Clinical trials have long been categorised as either explanatory or pragmatic (Schwartz and Lellouch 1967). Explanatory trials tend to be undertaken to assess the efficacy of an intervention under optimised conditions whilst pragmatic trials aim to determine the relative effectiveness of interventions within the environment in which they are going to be applied. In reality, there is a continuum between the two extremes (Sedgwick 2014). Pragmatically oriented trials have been increasing, supported by the desire to have evidence more likely to be translated to point of care. In the US, UK, Germany, Holland and Japan successful primary care networks have been set up, with general or other non-academic practitioners taking a key part in the research. Efforts to improve the design and efficiency of cariology trials do not seem to have been taken forward (Blackwelder 2004; Featherstone 2004).

Getting the choice of intervention and outcomes right

To make informed choices between treatment options in the clinical encounter, it is necessary to have a complete picture of how all available interventions perform against one another. Furthermore, the outcomes that are studied should be relevant to patients, and they must be similar enough across trials to allow synthesis of the data, informing the evidence base (Heneghan et al. 2017). If interventions are not compared to one another and similar outcomes are not measured, then it is not possible to synthesise the evidence. To look more closely at these issues, within the field of prevention and management of dental caries, we carried out systematic reviews of all RCTs over the last 50 years. Interventions and outcomes

were categorised and analysed (Levey et al. 2016, Levey et al. 2017, Schwendicke et al. 2017). Structured searching elicited 4774 articles and after screening titles, abstracts then full papers, 605 reports of RCTs were catalogued.

What do we investigate in cariology clinical trials? - Interventions

The strength of the overall evidence in any area of healthcare is governed by the extent to which the full range of relevant comparators have been investigated across the whole network of trials. This involves not only the interventions themselves but the relative comparator choice of intervention X against intervention Y. However, clinical trial design is often arbitrary, driven by happenstance, individual preferences or assumed relevance. Within cariology, the changing field has been driven by discoveries of novel remineralizing and biofilm modulating agents, new materials, and new treatment technologies (sealing in dental caries, for example). However, the overall strength of the evidence and the gaps in the field remain difficult to determine. Applying social network analysis, a mathematical modelling tool to evaluate the presence, strength or absence of relationships between the objects in the network (Rizos et al. 2011) allowed us to identify what has been investigated and helped clarify where gaps are. This revealed limitations in the evidence on the comparative effectiveness of caries prevention/management strategies (Schwendicke et al. 2017). Comparator choice seems to be driven by clinical indication (as might be expected). However, these limit conclusions on the true relative effectiveness of all strategies. There are still a variety of comparators that have not been, but should be, compared to one another. It also seems that comparisons within comparator classes (such as within various levels of invasiveness for the interventions) are preferred over comparisons between classes; for example, comparisons between Hall Technique crowns and standard restorations being preferred to comparisons of Hall Technique crowns with use of silver diamine fluoride. These choices might be clinically driven but they limit understanding of performance of the interventions compared to one another.

What do we measure in cariology trials? – Choice of outcomes

Inconsistent outcome reporting is a significant hurdle to combining results from trials into high quality systematic reviews (Ioannidis et al. 2017; Lamont et al. 2015). There is also the issue of selective outcome reporting resulting in bias, which is becoming acknowledged as a serious issue in medicine but has not yet been looked at in Dentistry (Ioannidis et al. 2017). Development and use of core outcome sets (COS) can reduce this barrier. A core outcome set is an agreed minimum set of outcomes that are included in the design of trials and allow data to be combined and compared at the systematic review stage. Our review of outcomes found a total of 1,364 outcomes reported in 605 published reports. We mapped outcomes reported in caries prevention and management RCTs as a first step to COS development, using systematic review methodology. Over the last 50 years, outcome reporting for clinical trials on prevention of caries and management of carious lesions have focussed on measuring “caries experience” and “restoration material clinical performance”, with “lesion activity” and “cost-effectiveness” increasingly being reported in more recent studies. Patient-reported and patient-focussed outcomes are becoming more common (as secondary outcomes) but remain low in use. The challenge with developing a COS will be anticipating outcomes relevant for the future based on trends from the past.

Examples of some challenges with intervention delivery fidelity, outcome analysis and intervention co-production are given in the following sections. Using two ongoing clinical trial, illustrations of the, sometimes hidden and unacknowledged, complexities with RCTs are explored.

FiCTION (Filling Children's Teeth: Indicated Or Not?) NIHR-HTA funded UK-wide trial

FiCTION (https://www.journalslibrary.nihr.ac.uk/programmes/hta/074403/#/) is a multi-centre primary dental care child-level, open RCT to determine the most clinically- and cost-effective approach to managing

caries in the primary dentition in the UK (Innes et al. 2013). The pilot trial began in 2009 (Marshman et al. 2012) and the main trial began in 2012, involving 72 dental practices and 1,124 children with dentinal caries (3-7 years-old on enrolment). Children are randomised to receive one of three caries management strategies (in a 1:1:1 ratio) and followed up over three years (Keightley et al. 2014; Stewart et al. 2015). The management strategies being used mean that it is not possible to blind the parents, children, or dentists as to which arm the child is participating in.

FiCTION has been commissioned to inform practice, teaching and funding of children's dentistry across the UK, with both quantitative and qualitative data incorporated within the outcomes. The primary outcome is incidence of pain and/ or dental infection. Secondary outcomes are: incidence of caries in primary and permanent teeth; quality of life; acceptability of treatment experiences to children and parents; and dentists' treatment preferences. The three treatment strategies for managing caries in the primary dentition are:

Arm 1: Conventional management of decay, with best practice prevention: Carious lesions are managed based on active treatment of caries by its complete removal. Local anaesthesia is placed, caries is mechanically removed using rotary instruments or by hand excavation and a restoration is placed. If the dental pulp is exposed during caries removal or there are symptoms of pulpitis, a pulpotomy may be carried out. Best practice prevention is carried out in line with current guidelines (see Arm 3).

Arm 2: Biological management of decay, with best practice prevention: Carious lesions are sealed into the tooth and separated from the oral cavity by an adhesive filling material over the decay, or by covering the tooth with a preformed crown using the Hall Technique. Decay may, on occasion, be partially removed prior to the tooth being sealed. Injections are rarely needed. Best practice prevention is carried out in line with current guidelines (see Arm 3).

Arm 3: Best practice prevention alone

Control of the biofilm through its frequent removal and low sugar intake can slow down carious lesion progression. For the best practice prevention alone arm, no caries removal, restoration placement or carious lesion sealing of primary teeth takes place. Treatment plans are based on best practice preventive care according to current UK guidelines. For primary teeth this involves three strands:

- Toothbrushing/ self-applied topical fluoride use;
- Dietary investigation, analysis and intervention; and
- Fluoride varnish application.

FiCTION trial's intervention delivery and adherence to protocol

Interventions applied over long periods of time in more pragmatically oriented clinical trials often suffer from difficulties with adherence to protocol. For FiCTION, monitoring how well practitioners had applied the three different trial arms over the three-year duration was important to be able to see where there had been drift or any "blurring" between arms. The direction and extent of deviations between arms is being monitored quantitatively through data collected from the dentists, explaining which arm the patient was moved to and why. This information will feed into the interpretation of the results by providing a basis for carrying out the intention to treat and the per protocol analyses.

There is no direct guidance on the thresholds for insufficient adherence to protocol for the arms to have been sufficiently implemented as intended. This is further complicated because each arm has multiple components. Should all component parts of the arms contribute equally to an episode of deviation or should they be weighted? A final complexity is added by the varying levels of treatment that are required

by the children in the trial. Within trials of medicinal products, the figure of 80% is often applied as a cut off for deciding on adherence if there is no rational basis for choosing a different figure. Because, clinically, this seemed reasonable, this has been taken as our cut-off for the FiCTION trial. A child having 21 tooth treatments throughout the trial with four teeth treated in a different arm will have had 81% adherence to the arm they were randomised to. However, if a child who only has one tooth treated in the trial has that single tooth treated away from arm, this is 0% adherence to protocol.

The process evaluation (Moore et al. 2015) has a qualitative component to allow more in-depth analyses of these deviations which should help to inform the implementation of FiCTION and explain the deviations from treatment that are seen, as these are not uniform across practitioners or between arms.

FiCTION trial's primary outcome: pain and infection

One of the biggest hurdles with trying to use clinical studies to underpin clinical decision making is that they often do not include thresholds of direct importance to patient care. The minimal clinically important difference is the smallest difference between interventions that a patient or dentist would consider adequate when choosing to use a new intervention (Make 2007).

At the start of the trial, the proposed primary outcome for FiCTION, was the proportion of children with at least one episode of dental pain and/or dental sepsis during the planned three year follow up period. The individual components of this composite outcome were to be considered as having equal importance (Cordoba et al. 2010). The outcome was going to be dichotomized: zero episodes of dental pain/ sepsis or at least one episode. As the trial progressed it became clear that the number of episodes experienced by a child was a more clinically relevant outcome and statistically a more sensitive measure. This was directly relevant to the minimal clinically important differences between the three treatment arms. The trial protocol was changed, re-appraised by the ethics committee and finalised as having co-primary outcomes through two analyses for the primary outcome data; 1) the proportion of children with at least one episode of dental pain and/or dental sepsis during the follow up period (incidence) using logistic regression, and 2) the total number of episodes of dental pain and/or dental sepsis for each child during the follow-up period using negative binomial regression. Because the original power calculation for the trial was based on a comparison of proportions, it remains the only powered analysis; however, an exploratory hypothesis test for the unpowered comparison of the mean number of episodes will be carried out and reported. The outcome data from FiCTION will be reported and published in 2018/9.

BRIGHT (Brushing RemInder 4 Good oral HealTh) NIHR-HTA funded UK-wide trial

Dental caries affects one in three, UK 12 year-olds and is closely linked to deprivation. Brushing with fluoridated toothpaste is a highly effective preventive measure and early establishment of self-care operation is associated with improved oral health through the lifecourse (Broadbent et al. 2016). Mobile health (mHealth) multimedia technologies interface with health care delivery most commonly involving mobile phones and making it a potential vehicle for health behaviour change (Head et al. 2013) with short messaging service (SMS) interventions showing robust effects on behaviours and outcomes (Head et al. 2013; Fjeldsoe et al. 2009). BRIGHT (https://www.journalslibrary.nihr.ac.uk/programmes/hta/1516608/#/) will evaluate the clinical and cost-effectiveness of a behaviour change programme to improve the oral health of young people living in deprived areas across the UK. It is a multi-centre, school based, assessor-blinded, two-arm cluster-randomised controlled trial with an internal pilot trial involving 5,760 young people (11-13 years-old). The BRIGHT intervention is a classroom-based, curriculum-embedded session and co-designed follow-up text messages, compared to routine education and no text messaging.

The primary outcome is incidence of carious lesions in permanent teeth (at three years). Secondary outcomes are: self-report frequency of daily tooth brushing; clinical assessment of plaque/gingivitis; Cost-effectiveness; and health- and oral health- related quality of life and oral health behaviours.

BRIGHT trial's intervention design

In the BRIGHT Trial, the intervention was pre-specified by the funder as a classroom based session and a series of follow-up text messages. The Keep on Brushing SMS programme, on which the funding call was based, had looked at unemployed 18-24 year olds in New Zealand (Schluter et al. 2015; Smith and Whaanga, 2015). The content of those messages was not appropriate for UK 11-13 year-olds. We adopted a co-design approach to the content of the SMS by using young people's own words, developed through the workshops to remind and reinforce the messages from the classroom based session. The assumption before carrying out the workshops had been that young people would be interested in being similar their friends, mimicking celebrities and interested in health. These were then presumed to be the factors that would be incorporated into the text message prompts. However, it became clear that the biggest factor that triggered interested in this topic was around avoiding disease rather than health and beauty; this was especially true when there was a "gory" part to the message, for example, one of the young people's developed and favoured messages was "On a daily basis, 100 million micro-creatures are swimming, eating, reproducing and depositing waste in your mouth". Designing interventions with the help of the target population can help to ensure the relevancy of it.

Conclusion

Although agreed as being a robust methodology for testing treatments, the RCT is expensive and acknowledged as being one of the most challenging to execute. Nevertheless, little attention has been paid to their design stage, and ensuring they are appropriate for use. Designing RCTs is a complex process that involves multiple stakeholders with multiple agendas. Decisions at the design and analyses stages will have a major impact on the quality and usability of the trial findings downstream. The designs of proposed clinical trials should be informed by evidence from the strengths and weaknesses of previous trials (Richards, 2011). In addition, gaps in research evidence can only become clear through evaluating what has already been studied. Once identified, gaps in the scope of research and research methodology should be addressed. There must be conversations and coordination between the major funders, researchers and end users of the research to ensure that the right interventions and the right outcomes with minimal clinically important differences are investigated.

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